PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 June 2000 (15.06.00)	
International application No. PCT/US98/20941	**Applicant's or agent's file reference** 434-204 PCT
International filing date (day/month/year) 14 October 1998 (14.10.98)	**Priority date** (day/month/year)
Applicant YANG, Danzhou et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 May 2000 (08.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: WARREN D. SCHICKLI
KING & SCHICKLI
3070 HARRODSBURG ROAD
SUITE 210
LEXINGTON, KY 40503

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NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	24 JAN 2001
Applicant's or agent's file reference: 434-204 PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US98/20941	14 OCTOBER 1998	NONE

Applicant: UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	DAVE NGUYEN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
434-204 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/20941	14 OCTOBER 1998	NONE
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 43/04; C12N 5/00 and US Cl.: 514/44; 435/455		
Applicant UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08 MAY 2000	17 DECEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer DAVE NGUYEN
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/20941

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-71 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims:
pages 72-74 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages 1-9 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/20941

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	2-3, and 6-9	YES
	Claims	1, 5, and 4	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-9	NO
Industrial Applicability (IA)	Claims	1-9	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 4, and 5 lack novelty under PCT Article 33(2) as being anticipated by either LETEURTRE et al. or GREEN ET AL.

LETEURTRE et al. teach a composition comprising an amount of complexes of GC-contained oligonucleotide fragments and camptothecin (CPT). *e.g.*, page 8956, column 2. LETEURTRE et al. teach that a close contact between guanine and CPT is required for the binding specificity of CPT to the GC of the oligonucleotide fragments, and that the complexes are involved in the formation of a transient covalent intermediate (page 8961, column 2).

GREEN ET AL teach a pharmaceutical composition comprising an antisense oligonucleotide and a CPT as a combined anti-cancer complex (column 8).

Absent evidence to the contrary, the composition of either LETEURTRE et al. or GREEN ET AL has all of the functional properties cited in the claims.

Claims 1-9 lack an inventive step under PCT Article 33(3) as being obvious over GREEN ET AL in view of applicant's admission over the prior art on pages 1, 2, 5 and 6 of the description.

GREEN ET AL teach a pharmaceutical composition comprising an antisense oligonucleotide and a CPT as a combined anti-cancer complex (column 8). In addition, GREEN ET AL teach that a delivery vehicle including conventional carriers, *e.g.*, liposomes, is employed to enhance the delivery of the oligonucleotide. While GREEN ET AL do not teach explicitly a method of using a conventional carrier including viral and non-viral vectors to carry the entire complex of the antisense oligonucleotide and any CPT known in the prior art (as indicated on pages 1 and 2 of the description), it is routine in the art for one of ordinary skill in the art to employ conventional carriers to deliver any known therapeutic agent (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
including CPT and antisense oligonucleotides to a tumor bearing host (pages 2, 5, and 6 of the description).

Thus, it would have been obvious for one of ordinary skill in the art to have employed convention carriers including viral and non-viral vectors to deliver a complex of any known CPT and an antisense oligonucleotide of GREEN ET AL to a host having a tumor. One of ordinary skill in the art would have been motivated to have employed any conventional carrier known in the art, as disclosed on pages 5 and 6 of the description, to deliver the therapeutic complexes cited in GREEN ET AL to a tumor site because GREEN ET AL teach that by employing a conventional carrier to deliver the disclosed antisense oligonucleotide, the growth of the transfected tumor will be sufficiently inhibited, and because it is routine in the art for one skilled in the art to have employed delivery vehicles including a lipid formulation in order to enhance the delivery of therapeutic agents including the CPT as disclosed in GREEN ET AL and on pages 1 and 2 of the description into a tumor cell, whereby a therapeutic
effect will be generated as the result of the use of the conventional delivery vectors.

Thus, the claimed invention as a whole was *primae facie* obvious.

Claims 1-9 meet the criteria set out in PCT Article 33(4) for industrial applicability.

Applicant's response (pages 2-5) filed 10 November 2000 has been considered by the authorized officer but is not found persuasive because of reasons set forth in the preceding paragraphs and because of the following reasons:

In response to Applicant's assertion (pages 2 and 3) that the LETEURTRE *et al.* reference does not address the specific chemical aspects of the bonding between camptothecin and DNA, and that based on the teachings provided in the LETEURTRE *et al.* reference, camptothecin readily hydrolyzes to form predominantly the carboxylate form, the comments are not found persuasive because the limitations of specific chemical aspects of the bonding between camptothecin and DNA are not recited in the claims and because Applicant has not provided factual evidence showing that the composition disclosed in the LETEURTRE *et al.* reference does not contain "sufficient amounts of active lactone form". Note that intended use of the claimed compositions is not relevant to the claimed products, particularly given the reasons set forth above.

In response to Applicant's assertion (pages 3 and 4) that GREEN *et al.* does not teach explicitly direct complexation of camptothecin and resultant stabilization of the active lactone, the comments are not found persuasive because the every limitation as recited in the claims is met by the compositions disclosed in GREEN *et al.*, and absent evidence to the contrary, the mixture of antisense oligonucleotides and camptothecin does contain a oligonucleotide-camptothecin complex. Applicant has not provided factual evidence showing that the composition disclosed in the GREEN *et al.* reference does not contain "sufficient amounts of active lactone form". Note that intended use of the claimed compositions is not relevant to the claimed products, particularly given the reasons set forth above.

In response to Applicant's assertion (pages 4 and 5) that since the GREEN *et al.* reference does not teach any advantage of the oligonucleotide-camptothecin complex for use in treating cancer, and that the combined cited references fail to provide any teaching or suggestion to lead one skilled in the art to the present invention as claimed, the comments are not persuasive because none of the presently pending claims recites any cancer treatment or any therapeutic effect as a result of the cancer treatment method. To the extent that the claims are readable on a delivery method of using well-recognized carrier disclosed in the prior art to enhance the delivery of the antisense oligonucleotide, the combined cited references do provide sufficient guidance for a skilled artisan to have a reasonable expectation of success to practice the oligonucleotide delivery method as claimed. Even with cancer treatment methods of using the antisense oligonucleotide, GREEN *et al.* does teach a pharmaceutical composition comprising an antisense oligonucleotide and a CPT as a combined anti-cancer complex (column 8).

---------- NEW CITATIONS ----------
NONE